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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,277	12/04/2003	Gary J. Rosenthal	42830-10010	7142

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EXAMINER	
ROBERTS, LEZAH	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,277	ROSENTHAL ET AL.	
	Examiner	Art Unit	
	Lezah W. Roberts	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4-12, 15, 17-25, 31, 35, 38, 41 and 133-141* is/are pending in the application.

4a) Of the above claim(s) *8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,9-12,15,17-25,31,35,38,41 and 133-141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *A and B*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's election of N-acetylcysteine as the pharmaceutical substance and a block copolymer comprising polyoxypropylene-polyoxyethylene as the biocompatible polymer in the reply filed on February 13, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1, 4-7, 9-12, 15, 17-25, 31, 35, 38, 41 and 133-141 will be examined on the merits.

Claim 8 is directed to a non-elected species.

Claim 8 is withdrawn from consideration.

Claims

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 20 contradict each other. The independent claim

stipulates the composition exhibit reverse-thermal viscosity behavior, yet the dependent claim reads the composition exhibits reversal-thermal viscosity behavior and does not exhibit reverse-thermal behavior. The composition either can exhibit one or the other, but it cannot exhibit both.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1) Claims 1, 4-7, 9-12, 15, 17-18, 21-23, 31, 35, 38, 41 and 133-136 are rejected under 35 U.S.C. 102(e) as being anticipated by Dobrozsi et al. (US 6,503,955).

Dobrozsi et al. teach pourable liquid vehicles comprising an aqueous or nonaqueous polymer solution. The vehicles comprise a polyoxyalkylene block copolymer, water and glycols. The copolymer comprises polyoxypropylene and polyoxyethylene and makes up 25% to 77% by weight of the vehicle, which encompasses claims 22-23. Water makes up 5% to 45% of the composition (col. 7,

lines 5-25). The glycols used, such as polyethylene glycol, which encompasses claim 31, make up 0 to 70% (col. 6, lines 50-53). The pourable liquid vehicle of the disclosed invention were formulated so that the contacting and mixing said vehicles to a mucosal surface of the body, or with some other fluid in the body, triggers the conversion of the pourable liquid vehicle to a more viscous gel-like mixture (col. 4, lines 33-48). The viscosities of the formulated vehicles were measured at room temperature and 37°C, the temperature inside the human body. It was disclosed the viscosity of the compositions increased at the higher temperature, therefore encompassing claims 1 and 18-19. The disclosed liquid compositions have a viscosity of less than about 7 pascal seconds, preferably less than about 2 pascal seconds, more preferably less than about 1 pascal seconds (col. 5, lines 12-17), which encompasses no larger than 60cP of the instant claims 133-141. The desired value of a composition's triggered viscosity ratio is least about 1.3, preferably at least about 2, more preferably at least about 5, and most preferably at least about 10. The triggered viscosity is defined as the viscosity of the gel divided by the viscosity of the liquid. Using this calculation the gel viscosity is greater than 80cP, which encompasses claims 133-141. The pourable liquid vehicles have a number of utilities including delivery of therapeutic agents. These include agents selected from the group consisting of antibacterial substances, antihistamines, anti-tussives, anti-inflammatories, expectorants/mucolytics, antioxidants, steroids, bronchodilators, antivirals, urinary tract disinfectives, antidiabetics, antineoplastics, antipsychotics, antihypertensives, muscle relaxants, antiprotozoals, and mixtures thereof (col. 7, lines 28-51) as recited in claim 4. Expectorants/mucolytics include N-

acetylcysteine as recited in claims 6 and 11-12. The active agents are added to the vehicles ranging up to 5% weight of the total composition according to the disclosed examples, which encompasses claim 15. The reference discloses several different dosage forms including tablets, capsules, elixirs, gels, rinses, dentifrices, lozenges, sprays, medicated lollipops, liquid filled capsules for intra-oral administration; gels, suspensions or solutions for intra-ocular or intra-aural administration; suppositories; and creams, ointments, gels, lotions and patches for topical application on the skin and scalp; and liquid suspension or solutions for injection by syringe, nasal gels, solutions, or suspensions for application into the nose with special applications or sprayers. These are also the types of composition used in the examples, which encompasses claim 41. Flavors and preservatives are also used in the disclosed compositions (see examples), as recited in claims 35 and 38. The reference anticipates the instant claims insofar as it discloses a composition comprising a therapeutic agent, a biocompatible polymer and carrier, where in the composition exhibits the reverse-thermal viscosity behavior over at least some range of temperature between 1°C and 37°C. In regards to claims such as 17, since the compositions of the reference are substantially the same, i.e. the range for the polymer is 25% to 77%, water ranges from 5% to 45% and glycol ranges from 0 to 70%, as the Applicant's compositions, the properties of the compositions such as the temperature where reverse-thermal viscosity behavior is exhibited should be substantially the same as the applicant's compositions, since the compositions of the reference and the compositions of the instant claims are substantially the same.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1) Claims 24-25, 133-135 and 137-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dobrozsi et al. (US 6,503,955).

The reference is discussed in detail above. The reference differs from the instant claims insofar as it does not disclose the compositions comprising 0.1 to 20% of the preferred block copolymer and the compositions were made when the liquid carrier was 5°C. The reference also differs from the instant claims insofar as it does not disclose specifically using N-acetylcysteine in an example as one of the therapeutic agents incorporated into the compositions for drug delivery, although the compound is listed in possible drug choices for the delivery vehicle.

It would have been obvious to adjust the compositions of the reference to meet the desired characteristics of the composition, such as viscosity as in claims 133-135 or

the removal of the reverse-thermal gelation property of claim 20, by adjusting the amount of copolymer used in the composition. Normally, changes in result effective variables are not patentable where the difference involved is one of degree, not of kind; experimentation to find workable conditions generally involves the application of no more than routine skill in the art. In re Aller 105 USPQ 233, 235 (CCPA 1955).

2) Claims 1, 4, 15, 17-19, 24-25 and 133-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dobrozsi et al. (US 6,503,955) in view of Stratton et al. (US 5,861,174).

The primary reference is disclosed in the anticipation section, subsection 1, above. The reference differs from the instant claims insofar as it does not disclose the compositions comprising 0.1 to 20% of the preferred block copolymer and the composition were made when the liquid carrier was 5°C.

Stratton et al. teach pharmaceutical compositions for the delivery of pharmacologically active proteins. The polypeptides make up 0.5% or greater of the disclosed compositions (col. 3, lines 38-45). In one embodiment of the invention, the polypeptide comprises 0.5 to 50% by weight of the compositions (col. 6, lines 46-50). The polymers of disclosed invention provide a sustained release delivery system for active agents or drugs (col. 1, lines 51-53). The delivery vehicle comprises block copolymers, polyoxyethylene-polyoxypropylene, namely Pluronic polyols, or poloxamers. Poloxamers have the ability to gel as a function of temperature and polymer concentration. Poloxamers having molecular weights below 10,000, do not

form gels at any concentration, therefore Pluronic F-127 and Poloxamer 407 are the polymers of choice for the disclosed invention (col. 2, lines 18-60), which encompass claims 138-139. These polymers have the characteristics of being liquid at temperatures below room temperature but will form a gel as they are warmed (col. 4, lines 38-41). The aqueous polymer solutions may be formed in two ways, by a cold process or by a hot process. The cold process involves dissolving the polymer at a temperature from about 5°C to 10°C (col. 5, lines 20-34). When adding the polypeptide, it is preferred to add the agent at a temperature of about 0°C to 10°C. These conditions encompass claims 24-25. Raising the sample temperature above the gel point of the poloxamer results in an even distribution of protein particles throughout the polymer gel (col. 6, lines 1-7). The copolymer will not form a gel at a concentration outside the range of 20% to 30% by weight, but it was discovered other compounds could be added to the compositions in order for the copolymer to form a gel at concentrations lower than 20% by weight, which encompasses claim 137. The reference differs from the instant claims insofar as it does not disclose comprising glutathione or its precursors and the viscosities of the compositions before and after the temperature change.

It would have been obvious to one of ordinary skill in the art to have used the delivery system and theory in the compositions of the primary reference motivated by the desire to provide a sustained release composition that exist in a liquid form and gels when introduced into the body wherein the therapeutic composition is released over a period of time, as disclosed by the secondary reference.

3) Claims 15, 22-23 and 136-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krezanoski (US 4,188,373) in view of Boggs (US 5,358,705).

Krezanoski teaches pharmaceutical delivery vehicles comprising polyoxyethylene-polyoxypropylene to deliver active agents to the mucous membrane. The polyoxyethylene-polyoxypropylene pharmaceutical vehicles of this invention have been unexpectedly found to increase drug absorption by the mucous membrane. Moreover, it has also been found that the pharmacologic response is unexpectedly prolonged. Drug action is typically both increased and prolonged by a factor of 2 or more. At the same time, protection is afforded to the involved tissues. A preferred polyoxyethylene-polyoxypropylene block copolymer for use in the pharmaceutical vehicle of this invention is one in which the number of polyoxyethylene units is about 70% of the total number of monomeric units in the molecule, as recited in claims 138-139. "Pluronic F-127" is such a material (col. 5, lines 23-61). The pharmaceutical compositions comprise from about 10% to about 26%, preferably from about 17% to about 26% of the copolymer and from about 74% to about 90% by weight water, the vehicle having a sol-gel or gel transition temperature in the range of from about 25°C to about 40°C, preferably from about 25°C to about 35°C, and especially from about 29°C to about 31°C (col. 3, lines 1-19), which encompasses claim 137. The reference differs from the instant claims insofar as it does not disclose the pharmaceutical agent is a precursor of or glutathione.

Boggs et al. teach oral composition for preventing conditions of the oral cavity. The active ingredient of the compositions include N-acetylcysteine complexes, which

makes up 0.05 to 10% of the compositions as recited in claims 15 and 136. These concentrations are considered "safe and effective", which is defined as an amount of compound or composition sufficient to induce a significant positive modification in the condition being treated, but low enough to avoid serious side effects (col. 4, lines 11-32). The reference differs from the instant claims insofar as it does not disclose using the active agent in a composition that exhibits thermal-reversible behavior.

It would have been obvious to one of ordinary skill it the art to have used the amounts of the therapeutic agents in the delivery systems of the primary reference motivated by the desire to increase drug absorption by the mucous membrane prolonging the pharmacologic response of the therapeutic agent as well as using the active in an effective amount and safe amount to treat conditions of the oral cavity as disclosed by the secondary reference.

Claims 1, 4-7, 9-12, 15, 17-25, 31, 35, 38, 41 and 133-141 are rejected.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lezah W. Roberts whose telephone number is 571-272-1071. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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